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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,224	03/02/2004	Yumi Matsuzaki	US-162	9934

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,224	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,9 and 10* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Claims 1, 3, 5-7, and 9-10 are pending in the application.

2. Applicant's amendment to the claims, filed on 5/25/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

3. Applicant's arguments filed on 5/25/2006 in response to the Office action mailed on 1/27/2006 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

4. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

5. Claims 5-7 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/13/2005.

6. Claims 1, 3, and 9 are being examined on the merits.

Claim Rejections - 35 USC § 112

7. Claims 1, 3, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

a. Claim 1 (claims 3 and 9 dependent therefrom) is indefinite in the recitation of "an activity of an arginine repressor" as it is unclear as the activity or activities of an arginine repressor that is/are intended as being reduced or eliminated. It is suggested that applicant clarify the meaning of the phrase "an activity of an arginine repressor." Furthermore, it is noted that the term "an activity of an arginine repressor is reduced or eliminated" is unclear absent a statement defining to what the activity is being compared. The term "an activity of an arginine repressor is reduced or eliminated" is a relative term and the claim should define and clearly state as to what the activity is being compared, i.e., reduced or eliminated activity in comparison to what level of activity?

b. Claim 3 is indefinite in the recitation of "said modification is..." as claim 1, from which claim 3 depends, recites two modifications – 1) a modification to reduce "an activity" of an arginine repressor and 2) a modification to enhance glutamine synthetase activity. It is suggested that applicant clarify the modification of claim 1 that is referred to in claim 3. In the interest of advancing prosecution, the claim has been interpreted as meaning modification to result in adenylation of GS being reduced or eliminated.

Claim Rejections - 35 USC § 112, First Paragraph

8. The written description rejection of claims 1, 3, and 9 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is overcome by amendment to claim 1 to require that the modification is reduced adenylation of glutamine synthetase or increased copy numbers of a gene encoding glutamine synthetase. According to applicant, such modifications are described in the specification and, when combined with the knowledge in the prior art, the specification adequately describes the claimed invention.

Applicant's argument is not found persuasive. The examiner maintains the position that the two disclosed species of the claimed genus fail to represent the wide variation within the genus of claimed modified coryneform bacteria. Claim 1 is drawn to a genus of coryneform bacteria having L-arginine or L-lysine-producing ability having *any* modification to reduce or eliminate adenylation of GS or increase copy number of a genus of genes encoding GS from any source that results in enhanced glutamine synthetase activity and *any* modification so that "an activity" of an arginine repressor is reduced or eliminated, wherein the arginine repressor comprises a protein that has at least 90% homologous (homologous is interpreted herein as meaning "identical") to SEQ ID NO:16. Claim 3 limits the modification that results in adenylation of glutamine synthetase being reduced or eliminated to a mutation at Y405 of SEQ ID NO:20 or a protein that is 90% homologous or more to SEQ ID NO:20. Claim 9 limits the bacterium of claim 1 to having a disruption in a gene encoding an arginine repressor. It should be

noted that the recited modifications are not limited to modification of DNA encoding glutamine synthetase or arginine repressor protein, but encompass other modifications, *e.g.,* modification to proteins that regulate GS activity or Arg repressor activity.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only two species of the claimed genus of coryneform bacteria, *i.e.,* strain 2256ΔargRΔglnE, also referred to as strain FERM BP-08630 and strain 2256ΔargRAde, also referred to as FERM BP-08631. Other than these two representative species, the specification fails to disclose any additional species of the claimed genus of coryneform bacteria, which, because the coryneform bacteria can have any modification that results in adenylation of GS being eliminated or reduced or any modification that results in increased copy numbers of a nucleic acid encoding GS from any source and any modification to reduce or eliminate "an activity" of an arginine

repressor, the genus encompasses widely variant species, which is undisputed by applicant. However, the specification discloses only two modifications that result in enhanced glutamine synthetase activity, *i.e.,* knockout of the *glnE* gene of SEQ ID NO:17 encoding adenylyltransferase by homologous recombination and mutation of the adenylation site of the glutamine synthetase of SEQ ID NO:20 at position 405. The specification discloses only a single modification of an arginine repressor to reduce or eliminate "an activity," *i.e.,* knockout of the *argR* gene of SEQ ID NO:15 by homologous recombination.

Given the lack of description of a representative number of modified coryneform bacteria, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

9. The scope of enablement rejection of claims 1, 3, and 9 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is overcome by amendment to claim 1 to require that the modification is reduced adenylation of glutamine synthetase or increased copy numbers of a gene encoding glutamine synthetase and modification to reduce or eliminate "an activity" of an Arg repressor. According to applicant, one of skill in the art, in view of the specification and the

knowledge and skill in the art, could make the full scope of claimed coryneform bacteria without requiring undue experimentation.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of claimed coryneform bacteria. The claims are so broad as to encompass coryneform bacteria having *any* modification that results in reduced or eliminated adenylation of GS or increased copy numbers of a nucleic acid encoding GS and any modification that results in "an activity" of an Arg repressor being reduced or eliminated. Also, the modifications are not limited to DNA encoding glutamine synthetase or arginine repressor protein, but broadly encompass other modifications as exemplified in Reference Example 1 beginning at p. 27 of the specification, wherein the activity of a protein that adenylates glutamine synthetase is reduced. As such, the scope of modifications encompasses modifications to proteins that modulate the activity of a glutamine synthetase and an arginine repressor. In view of the broad scope of the claims, a significant amount of non-routine experimentation is required to make all modified coryneform bacteria as encompassed by the claims. In this case, the specification discloses only two modifications that result in enhanced glutamine synthetase activity as encompassed by the claims, *i.e.,* knockout of the *glnE* gene of SEQ ID NO:17 encoding adenylyltransferase by homologous recombination and mutation of the adenylation site of the glutamine synthetase of SEQ ID NO:20 at position 405. The specification discloses only a single modification to reduce or eliminate "an activity" of an arginine repressor, *i.e.,* knockout of the *argR* gene of SEQ ID NO:15 by homologous recombination. The specification discloses only two

working examples of coryneform bacteria comprising these modifications, *i.e.*, strain 2256ΔargRΔglnE, also referred to as strain FERM BP-08630 and strain 2256ΔargRAde, also referred to as FERM BP-08631. Other than these working examples, the specification fails to provide any additional *specific* guidance for modifying a coryneform bacterium with an expectation of obtaining a bacterium having the desired activity/utility. The effects of modifying a bacteria, particularly modifications to nucleic acids encoding L-amino acid biosynthetic pathway enzymes and regulatory proteins thereof with an expectation of the bacteria maintaining the ability to produce a desired L-amino acid, is *highly* unpredictable as evidenced by Rhee et al. (cited in the 8/11/2005 Office action), Branden et al. (cited in the 1/27/2006 Office action) and Witkowski et al. (cited in the 1/27/2006 Office action).

In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of non-routine experimentation required, it is the examiner's position that undue experimentation is required for a skilled artisan to make the full scope of claimed bacteria.

Claim Rejections - 35 USC § 103

10. The rejection of claims 1, 3, and 9 under 35 U.S.C. 103(a) as being unpatentable over Suga et al. in view of Jakoby et al. and Nakayama et al. is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action.

RESPONSE TO ARGUMENT: Applicant argues that because Jakoby fails to teach or suggest improved Arg or Lys production by modifying a coryneform bacterium to enhance GS activity, one of ordinary skill in the art would not expect such an improvement when combined with a disrupted Arg repressor. Applicant further argues that the combination of increased GS activity and disruption of the Arg repressor has a synergistic effect on the production of Arg and Lys, which could not be predicted based on the combination of the cited references.

Applicant's argument is not found persuasive. Initially, it is noted that there is no requirement that Jakoby or any of the other references teach *enhanced or improved* Arg or Lys production as this limitation is not present in the claims. While it is acknowledged that Jakoby fails to expressly teach increased Arg or Lys production by a bacterium with enhanced GS activity, the examiner maintains the position that the *combination* of references of Suga, Jakoby, and Nakayama teach the claimed coryneform bacterium. Suga teaches a method of Arg production using a coryneform bacterium modified to have a knock-out of the Arg repressor gene, wherein the use of this modified bacterium results in a "markedly larger amount" of L-arginine (pp. 8-9) and that the nitrogen source in the medium used in the L-arginine production method of Suga is ammonium sulfate (p. 8-9). The reference of Jakoby teaches "[a] crucial step of amino acid production [by *C. glutamicum*]...is the assimilation of nitrogen" (p. 303, left column, bottom), that glutamine synthetase is a "central enzyme of nitrogen assimilation" (p. 305, left column, bottom) and that the activity of wild-type glutamine synthetase is significantly reduced in the presence of ammonium, while the activity of the Y405F mutant was not

downregulated in the presence of ammonium (p. 306, left column, top). The reference of Nakayama is cited as supporting Suga in use of ammonium sulfate as a nitrogen source in the coryneform bacterial production of Arg. Because assimilation of nitrogen is a crucial step in amino acid biosynthesis by coryneform bacteria, GS is a "central enzyme of nitrogen assimilation," and the activity of the mutant GS of Jakoby is not reduced in the presence of ammonium, one of ordinary skill in the art would have been motivated to express the modified GS of Jakoby in the cell of Suga for the production of Arg, particularly as the nitrogen source for coryneform bacterial production of Arg is ammonium as evidenced by Nakayama.

Regarding applicant's allegation of a synergistic effect, it is noted that MPEP 716.02 states, "[a]ny differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected." There is no dispute that the combination of a deletion of the Arg repressor and a modified GS appear to result in the increased production of Arg and Lys as compared to a strain with only a deletion of the Arg repressor (specification at p. 34). However, while applicant argues that the combination resulted in a synergistic effect (referring to Table 3 at p. 34 of the specification), it is noted that it appears that there is no way to determine whether a synergistic effect truly exists based on the results of Table 3. In order to determine whether a synergistic – as compared to an additive – effect was observed, it would appear that it is necessary to show Arg or Lys production levels using a strain with the modified GS (knockout or Y405F mutant) without the deleted Arg repressor. In this

case, there is no measure of Arg or Lys production using a coryneform strain overexpressing a modified GS as encompassed by the claims without deletion of the Arg repressor such that a determination of whether a synergistic effect of the combination on Arg or Lys production is or is not observed. MPEP 716.02(b) states, "[t]he evidence relied upon should establish 'that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.'" In this case, it would appear that the evidence fails to show a synergistic effect and an assertion of a synergistic effect would appear to be mere speculation. Applicant is reminded that, according to MPEP 716.01(c), "[t]he arguments of counsel cannot take the place of evidence in the record."

According to MPEP 2112.01.II, "'[p]roducts of identical chemical composition can not have mutually exclusive properties.' A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." Thus, even assuming *arguendo* a synergistic effect of the combination is shown by applicant, it is noted that this effect, absent evidence to the contrary, would have necessarily been an inherent result of using the cell of Suga with a knockout of the Arg repressor modified according to Jakoby to overexpress a Y405F mutant in the Arg production method of Suga.

Conclusion

11. Status of the claims:

Claims 1, 3, 5-7, and 9-10 are pending.

Claims 5-7 and 10 are withdrawn from consideration.

Claims 1, 3, and 9 are rejected.

No claim is in condition for allowance.

The amendment necessitated the new ground(s) of rejection set forth in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656